50. (Twice Amended) The system of claim 1, wherein a second type of modified surface layer is in contact with the microelectrode surface that separates the one or more electrically active cells and is repulsive to cell adherence.

REMARKS

Upon entry of these amendments, Claims 1-27 and 50 will be pending in the application.

The independent claims now specify that the intervening layer is in contact with the microelectrode surface. Support for this limitation is found on page 16, lines 23 – 27, and Figure 9 of the specification. Other changes to the independent claims merely clarify the language without adding new limitations. The changes to claims 22 and 50 are supported by the feature labeled "SM2" in Figure 9 and original claim 22. No new matter has been added.

Another newly executed Supplemental Declaration and Oath will be submitted shortly to replace the one filed with the last amendment, which had no page 2. An executed declaration under 37 C.F.R 1.132 will be submitted shortly to provide evidence on the physical structure of the Jung et al. device. Favorable reconsideration of this application is requested.

Claims 1-8, 12-14, and 23 stand rejected under 35 U.S.C. 102 (b) as being anticipated by Jung *et al.*

We previously argued that the device described by Jung et al. does not contain an intermediate layer attached directly to the microelectrode. The Examiner responded that "Assuming that this true (no evidence has been supplied demonstrating this for the prior art electrode), the claim as written does not require that the intervening layer be attached to or in contact with the microelectrode surface." The present amendment adds the limitation of the

intervening layer being in contact with the microelectrode surface. And a Rule 132 Declaration is being prepaid by one of the authors of Jung et al. (the inventor of this application) Prof. James Hickman that will provide evidence on the structure of the Jung *et al.* device. The Examiner is requested to defer examination of this RCE for at least six weeks to ensure that the Rule 132 Declaration is entered before taking further action.

The Examiner has pointed out that the data shown in Figure 6 (a, b) of Jung *et al.* appears to be the same as that in Figs 1A and 1B of the present application. These figures are the same, but that is no reason to conclude that the *embodiments covered by the pending claims* are the same as that disclosed in Jung *et al.* In fact, Figures 1A and 1B of this application did not arise from a device having the claimed intermediate layer. See, Hickman Declaration.

The Examiner states at page 4 of the Final Office Action that "the Jung *et al.* reference indicates that in some cases the platinization of the microelectrode was incomplete and thus the SAM could have attached to any hydroxyl groups on the exposed surface thus meeting the 'at least in the vicinity of said one or more cells' limitation." This phrase has been deleted from the claims.

Applicant agrees that the Jung *et al.* reference discloses the use of a silane SAM but not in the same way as claimed in Jung *et al.* because the microelectrode had been platinized using platinum black, which indicates that Jung *et al.* used the silane SAM on the insulator, not on the microelectrode. That is because the silane would not react with a platinized surface due to the absence of hydroxyl groups. See Hickman Declaration.

Therefore Jung *et al.* does not disclose or suggest putting an intervening layer attached to the microelectrode surface that provides a high impedance seal. In fact, Jung *et al.* teaches away

from that structure:

> These arguments show that small electrode impedances (Z_A and Z_B) and a large amplifier internal resistance (R_{IN}) provide the best coupling of the signal. In addition, *$R<<r$ implies that the cell should be placed directly on top of the electrode with little intervening material.* That is, there should be a small resistance, R, between cell and electrode, and a large resistance, r, between the cell-electrode junction and the bath. Regarding the micro-electrodes themselves, the platinum deposits, which have a very rough and porous morphology, both increase the capacitance C_{ma} (lowering the reactance [$X=-jl(\omega C_{ma})$] and *decrease the real part of the impedance R_{ma}*). *See*, page 1184, col. 2, lines 1-12 (emphasis added).

Hence, Jung *et al.* suggested that (i) there should be a small resistance between the cell and the electrode, and (ii) there should be a large resistance between the cell-electrode junction and the bath. The reference infers that both of these objectives are accomplished by placing the cells "directly on top of the *electrode with little intervening material.*" Jung *et al.* further stated that the platinum black deposits lower the reactance and decrease the real part of the impedance between the cell and the electrode.

Jung *et al.*'s interest, therefore, lies in decreasing the impedance between the cell and the electrode. This interest is served by depositing platinum black on the surface of the electrode while establishing little intervening material between the cell and the electrode.

Contrary to what the Examiner contends, not even a fortuitous amount of silane SAM would be established on the surface of platinum black because of the absence of surface hydroxyl groups – to which the silane SAM can covalently attach. And to address the Examiner's further contention, even if the coverage of the platinum deposits is incomplete, the underlying electrode described in Jung *et al.* is elemental gold – which, likewise, would fail to provide on its surface the functional groups necessary to react with the silane SAM.

In conclusion, no intervening layer within the meaning of the pending claims is possible

in the teachings of the Jung *et al.* reference. Applicant respectfully requests that this rejection be withdrawn.

Claims 1-14, 18-19, and 23-27 stand rejected as obvious over Borkholder *et al.* and Jung *et al.* However, Borkholder *et al.* would not have suggested modifying a device such as that of Jung et al by adding an intervening layer. Therefore it does not cure the deficiencies of the primary reference. Applicant respectfully requests favorable reconsideration of the rejected claims.

Claims 22, 23, 27 and 50 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The claims have been amended to provide more clarity. Applicant respectfully requests favorable reconsideration of the rejected claims.

With regard to the filing date of the provisional application, the Examiner contends that "the generic concept as disclosed in the instant specification and as recited in the claims is not disclosed in the provisional application." Applicant respectfully disagrees, as argued in some detail before. In any case, the applicant is not relying on the priority date to remove any prior art reference against the pending claims at this time, so there is no reason for the Examiner to make any priority determination. The Examiner should agree that the priority date question is moot.

No fees apart from the RCE fee are believed to be necessary. However, the Commissioner is authorized to charge any shortage in fees due in connection with the filing of this Amendment, or credit any overpayment, to Deposit Account No. 50-1710.

Respectfully submitted,

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Docket No.: 215177.00101
Customer No. 27160

HICKMAN
Application No. 09/575,377

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EXHIBIT A

MARKED VERSION OF THE CLAIMS
U.S. PATENT APPLICATION NO. 09/575,377

MARKED-UP VERSION OF CLAIMS SHOWING CHANGES MADE

1. (Once Amended) A system capable of identifying one or more ion channels of a cell, which elements are affected by a test substance, comprising a device and accompanying software,

in which said device comprises:

(a) a solid state microelectrode;

(b) a cell culture comprising one or more electrically active cells having a cell membrane including one or more ion channels, which one or more cells are capable of providing a measurable action potential that exhibits one or more perceptible characteristics in response to a test substance; and

(c) an intervening layer in contact with the microelectrode surface, which (i) comprises a surface modifying agent, and (ii) is positioned between said microelectrode and the one or more cells of said cell culture, [such that] that provides a high impedance seal with [is provided at least in the vicinity of] said one or more cells of said cell culture,

and in which said accompanying software comprises instructions that can be implemented by a computer and which are capable of relating changes in the one or more characteristics exhibited by said action potential to one or more ion channels of said one or more cells upon exposure of said one or more cells to a test substance.

15. (Twice Amended) A system capable of identifying one or more ion channels of a cell, which elements are affected by a test substance, comprising a device and accompanying software,

in which said device comprises:

(a) a solid state microelectrode;

(b) a cell culture comprising one or more electrically active cells having a cell membrane including one or more ion channels, which one or more cells are capable of providing a measurable action potential that exhibits one or more perceptible characteristics in response to a test substance; and

(c) an intervening layer in contact with the microelectrode surface which (i) comprises a surface modifying agent, and (ii) is positioned between said microelectrode and the one or more cells of said cell culture, [such that] that provides a high impedance seal with [is provided at least in the vicinity of] said one or more cells of said cell culture, said intervening layer further comprising cell anchorage molecules;

and in which said accompanying software comprises instructions that can be implemented by a computer and which are capable of relating changes in the one or more characteristics exhibited by said action potential to one or more ion channels of said one or more cells upon exposure of said one or more cells to a test substance.

17. (Twice Amended) A system capable of identifying one or more ion channels of a cell, which elements are affected by a test substance, comprising a device and accompanying software,

in which said device comprises:

(a) a solid state microelectrode;

(b) a cell culture comprising one or more electrically active cells having a cell membrane including one or more ion channels, which one or more cells are capable of providing a measurable action potential that exhibits one or more perceptible characteristics in response to a test substance; and

(c) an intervening layer in contact with the microelectrode surface which (i) comprises a surface modifying agent, and (ii) is positioned between said microelectrode and the one or more cells of said cell culture, [such that] that provides a high impedance seal with [is provided at least in the vicinity of] said one or more cells of said cell culture, said intervening layer further comprising a high viscosity mixture comprising alcohols, ethers, esters, ketones, amides, glycols, amino acids, saccharides, carboxymethylsaccharides, carboxyethylsaccharides, aminosaccharides, acylaminosaccharides, polymers thereof, or combinations thereof;

and in which said accompanying software comprises instructions that can be implemented by a computer and which are capable of relating changes in the one or more characteristics exhibited by said action potential to one or more ion channels of said one or more cells upon exposure of said one or more cells to a test substance.

20. (Twice Amended) A system capable of identifying one or more ion channels of a cell, which elements are affected by a test substance, comprising a device and accompanying software,

in which said device comprises:

(a) a solid state microelectrode;

(b) a cell culture coated with a polymer comprising one or more electrically active cells having a cell membrane including one or more ion channels, which one or more cells are capable of providing a measurable action potential that exhibits one or more perceptible characteristics in response to a test substance; and

(c) an intervening layer attached to the microelectrode surface which (i) comprises a surface modifying agent, and (ii) is positioned between said microelectrode and the one or more cells of said cell culture, [such that] that provides a high impedance seal with said one or more cells of said cell culture;

and in which said accompanying software comprises instructions that can be implemented by a computer and which are capable of relating changes in the one or more characteristics exhibited by said action potential to one or more ion channels of said one or more cells upon exposure of said one or more cells to a test substance.

23. (Twice Amended) The system of claim 1, in which said device further comprises (d) a detector circuit.

24. (Twice Amended) A method of determining one or more ion channels of a cell that are affected by a test substance, comprising:

(a) contacting a substance to be tested with a device comprising a solid state microelectrode; a cell culture including one or more cells having a cell membrane including one or more ion channels, which one or more cells are capable of providing a measurable action potential that exhibits one or more perceptible characteristics in response to a test substance; an intervening layer in contact with the microelectrode surface that provides [is acting as] a high impedance seal and which is positioned between said microelectrode and said cell culture,

(b) collecting data on the action potential, the one or more characteristics thereof, or one or more changes therein; and

(c) determining from said data the one or more ion channels that are affected by the test substance.

50. (Twice Amended) The system of claim 1, wherein [which further comprises] a second type of modified surface layer is attached to the microelectrode surface that separates the one or more electrically active cells and [which comprises a layer that] is repulsive to cell adherence.